Remarks

Claims 44 and 52-56 are pending. Claims 44 and 52-56 are rejected. Claim 44 is currently amended. Support for the amendments to Claim 44 can be found at, for example, paragraphs [0014], [0050], [0054], [0055], [0064] and Fig. 1 of the original application. The amendments are believed to place the claims in better condition for allowance, or alternatively for appeal, and entry of the amendments is respectfully requested.

An objection has been made to the specification. The objection is to the amendment to the specification filed February 25, 2008 and is made under 35 USC §132(a) and states that the amendment introduces new matter into the disclosure. The Applicants have amended the specification at paragraph [0064] on page 17 as indicated only for the sake of compact prosecution and believe the new matter rejection is without merit.

Claims 44 and 52-56 have been rejected under 35 USC §112 as containing new matter. The rejection does not explicitly identify the new matter. However, Claim 44 was previously amended to recite "comprising antigens from an autologous inactivated, non-recombinant human immunodeficiency virus isolated from blood tissue[.]"

Amended Claims 44 and 52-56 do not contain new matter and comply with the written description requirement of 35 USC §112, first paragraph. Independent Claim 44 has been amended to recite: "2,2'-dithiopyridine-inactivated human immunodeficiency virus is an autologous virus and is isolated from blood tissue[.]" Claims 52-56 are dependent on independent Claim 44 and include all of its recitations. Claims 52-56 have not been independently amended.

Amended Claim 44 does not contain new matter and is fully supported by the originally filed application. For example, the recitation in amended Claim 44 of a "therapeutically effective amount of patient dendritic cells, said dendritic cells being loaded with 2,2'dithiopyridine-inactivated, non-recombinant human immunodeficiency virus" is clearly supported by paragraph [0050] on page 13 of the originally filed application. This paragraph teaches that in one aspect of the disclosure "the DCs [dendritic cells] of HIV infected patients loaded with AT-2 [(2,2'dithiopyridine)]-inactivated autologous HIV, will elicit functional virus-specific effector CD8+ T lymphocytes[.]"

The process steps for obtaining the dendritic cells is clearly supported by paragraphs [0054] and [0055] at page 14 of the originally filed application. These paragraphs describe a

well known, art recognized, non-species specific protocol for obtaining dendritic cells from blood tissues of a patient.

Furthermore, the recitation in amended Claim 44 that the "autologous virus ... is isolated from blood tissue" is clearly supported by paragraph [0014] on page 7, paragraph [0064] on page 17, Example 1 on page 17 and Fig. 1 of the application. Paragraph [0064] on page 17 states "[v]iruses were isolated from 10 untreated asymptomatic HIV-seropositive patients (CD4 cell count, 200 to 600 cells/μl; plasma HIV RNA load, 4 to 6 $\log_{10}$ eq copies/ml) and 20 patients treated by prolonged HAART (>3 years) (CD4 cell count, 300 to 700 cells/μl; 10 patients with virologic response [plasma HIV RNA load, <50 $\log^{10}$ eq copies/ ml] and 10 patients with virologic resistance [plasma HIV RNA load, 4 to 6 $\log^{10}$ eq copies/ml]). (FIG. 1)." A person of ordinary skill in the art would also instantly recognize from Example 1, paragraph [0064] on page 17, paragraph [0014] on page 7 as well as Fig. 1, that the HIV viruses that are isolated from the patients are "isolated from blood tissue[.]" This is because the examples state that the viral titer measured is the viral titer in "plasma" which is clearly isolated from blood tissue. This point is underscored by examination of Fig. 1 which shows that the isolated viral load is "plasma viral load ($\log_{10}$ eq copies/ml)[.]" This information makes it abundantly clear that the HIV viruses being isolated are from plasma--a blood tissue--and are autologous viral particles.

Furthermore, the teachings of Lu and Andrieu (75 J. Virol. 8949 (2001)) provide further confirmation that one of ordinary skill in the art would understand this. Indeed, Lu and Andrieu describe the experimental work underlying, and described in the application. This experimental work confirms the identity between the patients (*compare* Table 1 of the publication and Fig. 1 of the application), the method for the preparation of the dendritic cells and the results obtained. This publication also describes more precisely and with a high degree of detail the method used for isolating the virus. In fact, this publication states "[v]iruses were isolated by coculture of phytohemagglutinin (Sigma, St. Louis, MO) stimulated HIV-negative donor peripheral blood mononuclear cells (PBMC) with patient CD4+ T cells[.]" *See* Lu and Andrieu at page 8950. This teaching should also be interpreted in context with Chun *et al.* (5 Nat. Med. 651 (1999)) which is referenced and teaches that patients' CD4+ T cells are isolated from peripheral blood when it states "[v]irus could not be isolated from the peripheral blood CD4+ T cells in three patients receiving IL-2 plus HAART, despite the fact that large numbers of resting CD4+ T cells were cultured[.]" *See* Chun *et al.* at abstract.

Altogether, the above confirms that the CD4+ T cells of the patient in the application are peripheral blood T cells and, consequently, that the virus is from blood tissue. Importantly, the teachings of both of these documents are incorporated by reference into the originally filed application. As a whole, this information makes it clear that amended Claim 44 is fully supported by the disclosure in the originally filed application and that one of ordinary skill in the art would recognize that the subject matter recited is taught in the originally filed application. Additionally, the Applicants note that amended Claim 14 is also consistent with the amendments which were previously entered and which did not garner a new matter rejection.

Claim 44 stands rejected under 35 U.S.C. §103 as being obvious over Belardelli. The Applicants also note with appreciation the Examiner's detailed comments hypothetically applying Belardelli to Claim 44. Additionally, the Applicants note the rejection essentially states that the prior arguments and the Declaration of Professor Marie-Lise Gougeon were ignored. The Applicants nonetheless respectfully submit that Belardelli fails to provide disclosure that would render amended Claim 44 obvious. Reasons are set forth below.

Belardelli does not teach all the elements of Claims 44 and 52-56. Claim 44 recites that the claimed pharmaceutical composition comprises "a therapeutically effective amount of patient dendritic cells, said dendritic cells being loaded with 2,2'-dithiopyridine-inactivated, non-recombinant human immunodeficiency virus, and a pharmaceutically acceptable carrier; wherein the 2,2'-dithiopyridine-inactivated human immunodeficiency virus is an autologous virus and is isolated from the blood tissue of said patient[.]" Claims 52-56 are dependent on Claim 44. Belardelli teaches at paragraph [0164] that the dendritic cells described therein received "HIV-1 SF162 strain [which] was inactivated by AT-2." Cheng-Mayer *et al.* (86 PNAS 8575 (November 1989) (hereinafter "Chen-Mayer")) describes the isolation and phenotypic characterization of the HIV-1 SF162 virus from an unknown patient over 18 years ago. Importantly, Cheng-Mayer teaches that the HIV-1 SF162 virus used in Belardelli is not an autologous HIV virus isolated from the blood tissue of the individual patient to be treated with the dendritic cells, but instead is a non-autologous virus isolated from blood free, cerebrospinal fluid (CSF). Consequently, Belardelli does not teach all the elements of amended Claims 44 and 52-56 and one of ordinary skill in the art would be unable to use the teachings of Belardelli to achieve the claimed subject matter. Stated differently, the rejection fails to establish the third element of *prima facie* obviousness which requires that the cited prior art reference, or references, teach all the elements of the claimed subject matter.

The Applicants agree with the Examiner's frank acknowledgment that it was not readily apparent from the disclosure in Belardelli that the virus used is non-autologous. The rejection, however, states that it would have been *prima facie* obvious for one skilled in the art to use autologous HIV. In particular, the rejection specifically states:

> However, due to the many variability in the many type of HIV isolates and the ability of the virus to mutate, it would have been prima facie obvious for one of ordinary skill in the art, at the time the invention was made, to use autogolous HIV. One of ordinary skill in the art, at the time the invention was made, would have been motivated to do so to induce immune response against the specific HIV isolate infecting the subject. One of ordinary skill in the art, at the time the invention was made, would have had a reasonable expectation of success for doing so because the use of autogolous antigens is routinely practiced in the art.

The Applicants respectfully submit that this portion of the rejection is mere speculation that is not supported by any fact on the record. There are a number of ways that this speculative statement manifests itself. Several of those ways are highlighted below.

The Applicants first note that Belardelli relates to the study of properties of (IFN). That is different from the Applicants' objective to provide a composition for treating immunodeficiency viruses. This alone is completely different.

Belardelli itself admits that culturing dendritic cells with GM-CSF and IL-4 is inadequate. This can be seen by reference to page 2, paragraphs [0020] and [0021]. A portion of the relevant text is reproduced below for the Examiner's convenience:

> DCs produced according to this procedure, however, display features of and behave as immature DCs expressing low levels of CD80 and CD86. Consequently, these DCs act as weak stimulators of a specific T cell response and MLR. In this setting, further DC maturation can be driven by the addition of TNFα, IL-1, LPS, monocyte-conditioned medium (22) or sCD40L for two additional days (2, 3).
>
> Thus, the requirement of a further step for DC maturation by addition of other factors to immature DCs represents a strong limitation for the rapid generation of DCs highly effective for clinical purposes.

Furthermore, Belardelli states that:

> Virus-pulsed IFN[/GM-CSF]-DCs not only proved to be better stimulators of ^{3}H-thymidine uptake by autologous PBLs than IL-4[/GM-CSF]-DCs, but also induced a stronger Th1-oriented response.

See Belardelli at paragraph [0166] and Fig. 9. Clearly, Belardelli is teaching away from using autologous dendritic cells stimulated with IL-4/GM-CSF and would not motivate one of ordinary skill in the art.

In summary, Belardelli teaches away from the claimed compositions and that culturing with GM-CSF and IL-4 is not good enough. At best, this results in immature dendritic cells which require <u>further</u> treatment for proper dendritic cell maturation. The Applicants respectfully submit that this admission is hardly suggestive to those skilled in the art to employ this technique. Instead, Belardelli employs further treatment to achieve his goals. This is succinctly stated in Belardelli on page 2 in paragraph [0024] which states:

> ...partially mature DCs are obtainable thereby from freshly isolated monocytes after a single step treatment including type I IFN as an essential factor.

In other words, other treatments are effective in the Belardelli protocol because Belardelli realizes that culturing with GM-CSF and IL-4 is quite weak and only results in immature dendritic cells.

Another problem with Belardelli is that there is no discussion of a therapeutic vaccine and, as a consequence, the origin of the virus or the dendritic cell is not considered. Thus, Belardelli provides no teachings which would be of use to one skilled in the art to select autologous or heterologous cells or viruses. As a consequence, the Applicants respectfully submit that the Applicants' claimed use of GM-CSF and IL-4 would hardly be obvious inasmuch as Belardelli actually leads those skilled in the art away from such a treatment. This is underscored by Example 1, Fig. 1, Fig. 2 and Table 1 of Belardelli which clearly demonstrate the phenotypic and functional differences between IFN/GM-CSF treated cells and IL-4/GM-CSF treated cells.

Yet another problem is that many therapeutic vaccines are developed that are not autologous. Thus, there is plenty of opportunity for those skilled in the art to pursue other

means. This is particularly compelling in view of the above statements wherein the Applicants' claimed culturing with GM-CSF and IL-4 is deemed by Belardelli to be inadequate.

However, the Applicants provide further evidence of non-obviousness. In that regard, the Applicants refer to the previously entered Declaration of Professor Marie-Lise Gougeon who is well known in the field of HIV/AIDS treatment and respectfully request that this Declaration now be given full consideration.

Professor Gougeon does not believe that it would have been *prima facie* obvious to use autologous HIV and does not believe that one skilled in the art would have been motivated to do so based on the Belardelli disclosure which admits to the inefficiencies of the GM-CSF and IL-4 culturing methodology. Therefore, Professor Gougeon does not believe that one skilled in the art would have had a reasonable expectation of success. Obviousness rejections cannot be maintained in the absence of a reasonable expectation of success. Withdrawal of the rejection is respectfully requested.

The rejection also improperly relies on an inherency type argument to establish that Belardelli teaches all the elements of the claims for purposes of attempting to establish *prima facie* obviousness. This is because the rejection clearly states that "the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable." In other words, the rejection acknowledges that Belladelli does not expressly teach all the elements of the claimed compositions.

The rejection also improperly cites a number of cases such as Atlas Powder Co. v. Ireco Inc., In re Best and In re Crish to support the conclusion that the claimed subject matter is obvious because Belardelli inherently teaches all the elements of the claims. *See* Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342 (Fed. Cir. 1999); In re Best, 562 F.2d 1252 (CCPA 1977); and In re Crish, 393 F.3d 1253 (Fed. Cir. 2004). This is inappropriate because Atlas, Best, and Crish all stand for the proposition that the doctrine of inherent anticipation can be applied in the context of 35 USC §102, but do not hold that inherent anticipation can be applied in the context of 35 USC §103 obviousness rejections. Moreover, it is self evident to state:

> "That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *See* In re Spormann and Heinke, 150 USPQ 499, 452 (CCPA 1996) (emphasis added).

This means the rejection fails to establish that Bellardelli teaches all the elements of the claims.

Furthermore, the rejection improperly concludes that the compositions of Bellardelli are necessarily "the same as instantly claimed" by the Applicants. This is because the process by which the Applicants' compositions and those of Belardelli are made are different. For example, the Applicants stimulate cells purified by plastic adherence with 2,000 U/ml of GM-CSF and 50 ng/ml IL-4, while Belardelli stimulates cells purified by electronic gating using a FACSort fluorescence activated cell sorter with 500 U/ml of GM-CSF and 500 U/ml of IL-4. Clearly, the Applicants' process and that of Belardelli are different and would not necessarily result in dendritic cells having exactly the same properties such as the ability of the claimed composition to "expand[] *in vivo* expression of virus-specific CD8+ T-cells, and said virus-specific CD8+ T-cells kill HIV-infected cells." This is underscored by the teachings of Belardelli itself and numerous other examples in the art which clearly demonstrate that apparently "minor" differences in cell stimulation product substantial phenotypic and functional differences in the resulting cells. *See e.g.* Belardelli at Fig. 4..

Claims 52-56 stand rejected under 35 U.S.C. §103 over the combination of Lu with Belardelli. The Applicants respectfully submit that Lu does not provide teachings that would cure the deficiencies set forth above with respect to Belardelli. Accordingly, even if one skilled in the art were to make the hypothetical combination, the compositions would still not result in the subject matter of Claims 52-56. Withdrawal of the rejection is respectfully requested.

Claims 43-44, 46 and 52-56 stand provisionally rejected based on obviousness-type double patenting over Claims 2, 7 and 13 of co-pending Application No. 11/243,094. Inasmuch as this is a provisional rejection, the Applicants respectfully request that further treatment of this rejection be held in abeyance pending withdrawal of the other rejections.

In light of the foregoing, the Applicants respectfully submit that the entire application is now in condition for allowance, which is respectfully requested.

Respectfully submitted,

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